REMARKS

Sequence Compliance

The Examiner contends that the specification contains sequence disclosures that have not been identified in the text of the application. Specifically, the Examiner refers to the figure legends for Figs. 1 and 5 on pages 4-5 and asserts that these should be amended to recite the appropriate sequence identifiers and the appropriate positions with regard to SEQ ID NO:1. The Examiner further asserts that similar sequence issues should be addressed on pages 3, 6 and 7 as well as on pages 14 and 19 of the specification.

Initially, Applicants note that it appears that the Examiner has overlooked Applicants' submission of November 4, 2002, wherein many of the issues set forth above were addressed by Preliminary Amendment. Specifically, the legends for Figs. 1 and 5 have already been amended to recite the appropriate sequence identifiers, and amendments also were made to the sections referenced on pages 6, 14 and 19. For the Examiner's convenience, a copy of this Preliminary Amendment is enclosed herewith. In view of the Examiner's comments above, Applicants have reviewed the sections noted by the Examiner and present some additional amendments on pages 3, 6 and 7 to insert the appropriate sequence identifiers.

Applicants respectfully submit that the specification is fully compliant with 37 CFR 1.821-1.825. The Examiner's reference to a restriction requirement on page 2 of this Office Action appears to be a typographical error, since there is no restriction requirement in the October 6 Office Action.

Objection to Claim 12

The Examiner has indicated that Claims 1, 9-10 and 12-13 are allowed, but suggests an amendment to Claim 12 to clarify the claim language. Claim 12 has been amended as suggested by the Examiner.

Objection to Claim 11

The Examiner has objected to Claim 11 as allegedly being of improper dependent form. Specifically, the Examiner contends that this claim is broader than base Claim 1.

Applicants traverse the Examiner's objection to Claim 11 since, because it depends from Claim 1, Claim 11 must carry forth all of the limitations of Claim 1 (i.e., the claimed sequence must carry the mutation described in Claim 1 and it also must further limit the sequence of (a) or (b) of Claim 1). Nonetheless, in order to expedite prosecution, Applicants have amended Claim 11 to reiterate the limitations of Claim 1 and to clarify the claim. The amendment is fully supported by the present claims (i.e., Claim 1). Applicants submit that the claim, as amended, clearly is in proper dependent format.

Rejection of Claim 11 Under 35 U.S.C. § 112, First Paragraph:

The Examiner has rejected Claim 11 under 35 U.S.C. § 112, first paragraph, on the basis of written description. Specifically, the Examiner asserts that there is no description in the instant specification as to what constitutes sequences *comprising* unknown and undescribed promoter sequences.

Applicants traverse the Examiner's rejection of Claim 11. Claim 11 previously incorporated all of the limitations of Claim 1, and has now been amended to clarify this relationship. Specifically, Claim 11 refers to the fragment of Claim 1, wherein said fragment is an at least 10 nucleotide fragment of the sequence *consisting of* SEQ ID NO:1 and containing the recited C-G substitution mutation. Claim 11 simply further defines this fragment of *definite structure* by stating that it must further include at least positions 2420 to 2443 of SEQ ID NO:1. This is not inconsistent with the fragment in Claim 1 and describes a more limited fragment than that of Claim 1 because now the fragment must include at least positions 2420 to 2443 of SEQ ID NO:1. The specification fully describes nucleotide sequences consisting of SEQ ID NO:1 and at least 10 nucleotide fragments of SEQ ID NO:1 containing the recited substitution mutation, and so of course the specification also fully describes such fragments that contain at least positions 2420 to 2443 of SEQ ID NO:1.

In view of the foregoing discussion, Applicants respectfully request that the Examiner withdraw the rejection of Claim 11 under 35 U.S.C. § 112, first paragraph.

Rejection of Claim 11 Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected Claim 11 under 35 U.S.C. § 112, second paragraph, contending that this claim is indefinite because it is allegedly ambiguous whether a C-G substitution is envisioned for this dependent claim since it was not recited.

In reply, Applicants submit that because Claim 11 depends from Claim 1, it automatically incorporates all of the limitations of Claim 1, which include the C-G substitution, and therefore is clear as previously presented (i.e., the limitations of Claim 1 are implicit in all dependent claims). However, to expedite prosecution, Applicants have amended Claim 11 to import the limitations of Claim 1 as an explicit recitation.

In view of the foregoing discussion, Applicants respectfully request that the Examiner withdraw the rejection of Claim 11 under 35 U.S.C. § 112, second paragraph.

Rejection of Claim 11 Under 35 U.S.C. § 102(b):

The Examiner has rejected Claim 11 under 35 U.S.C. § 102(b), contending that this claim is anticipated by Parks et al. for the reasons of record (i.e., contending that Parks et al. teach a sequence comprising positions 2420-2443 of SEQ ID NO:1).

Applicants traverse the Examiner's rejection. As stated above, Claim 11 in its prior form implicitly contained all of the limitations of Claim 1 and therefore can not be anticipated by Parks et al., because Parks et al. do not teach or suggest the nucleotide sequence of Claim 1. Claim 11 has now been amended to clarify that it further limits the sequence of Claim 1. Parks et al. do not teach or suggest the sequence of Claim 11. Therefore, Applicants respectfully request that the Examiner withdraw the rejection of Claim 11 under 35 U.S.C. § 102(b).

Applicants have attempted to respond to all of the remaining issues as set forth in the October 6 Office Action and submit that the claims are in a condition for allowance. To expedite prosecution and allowance of these claims, the Examiner is encouraged to contact the below-named agent at (303) 863-9700 to discuss any remaining issues.

Respectfully submitted,

SHERIDAN ROSS P.C.

By: Angela Sebor

Angela Dallas Sebor
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1560 Broadway, Suite 1200
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(303) 863-9700

Date: December 6, 2004

COPY

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re the Application of:	Group Art Unit: 1647
ALBERT et al.	Examiner: Hayes, Robert Clinton
Serial No.: 09/430,412	RESPONSE TO COMMUNICATION AND PRELIMINARY AMENDMENT
Filed: October 29, 1999	
Atty. File No.: 2268UO-1	
For: "MUTATIONS OF THE 5' REGION OF THE HUMAN 5-HT1A GENE, ASSOCIATED PROTEINS OF THE 5' REGION AND A DIAGNOSTIC TEST FOR MAJOR DEPRESSION AND RELATED MENTAL ILLNESSES"	

CERTIFICATE OF MAILING

I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS FIRST CLASS MAIL IN AN ENVELOPE ADDRESSED TO THE COMMISSIONER FOR PATENTS, WASHINGTON, DC 20231 ON 11/4/02.

SHERIDAN ROSS P.C.

BY: Barbara Russell

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

This response is filed in response to the Communication from the Examiner mailed October 2, 2002 regarding the Sequence Listing for the above-identified patent application. This response is believed to be timely and therefore, no fees are enclosed. In the event that fees are due in connection with this response, please debit Deposit Account No. 19-1970.

Prior to the Examiner's review of the above-identified application on the merits, please enter the following Preliminary Amendment.

IN THE SPECIFICATION:

On page 1, immediately following the title of the application, please add the following new subheading and paragraph:

--CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of priority under 35 U.S.C. § 119(e) from U.S. Provisional Application Serial No. 60/106,375, filed October 30, 1998.--

On page 4, please replace the paragraph spanning lines 15-18 with the following new paragraph:

--These and other features of the invention will become more apparent from the following description in which reference is made t the appended drawings wherein:

FIGURE 1a, 1b and 1c shows the promoter region of human 5-HY1A from -3438 to -393 (SEQ ID NO:1). The position of the polymorphism at -1017 is shown by an arrow.--

Please replace the paragraph spanning page 5, line 18 through page 6, line 2, with the following paragraph:

--**FIGURE 5** shows the detection of the C-G polymorphism at -1017 bp of the 5-HT1A gene in human blood samples. Fig. 5A is the wild type sequence with a C at position -1017. Fig. 5B shows a heterozygous individual for the mutation, with both a C and G at position -1017 bp. Fig. 5C is the homozygous mutant sequence, showing a G at position -1017. The repressive region of the human 5-HT1A promoter was analyzed for length and size variations using blood samples from depressed patients and normals. A 718-bp fragment was amplified by PCR and sequenced within the region of the promoter between -1593 to -876 bp of the initial ATG codon. Shown is DNA sequence analysis in the region of -1017 bp from PCR products of 3 different patients which revealed patients with: the wild-type sequence **A** (figure shows positions 2411-2433 of SEQ ID NO:1), with a C at position -1017 from the initial ATG codon; sequence heterozygous for the mutation with both a C and a G nucleotide at -1017 bp, corresponding to sequence **B** (figure shows positions 2411-2433 of SEQ ID NO:1 with the indicated mutation shown at position 2422); and sequence homozygous for a C-G mutation (sequence **C**) (figures shows positions 2411-2433 of SEQ ID NO:1 with the mutation shown at position 2422) .--

On page 6, please replace the paragraph spanning lines 17-25 with the following paragraph:

--The present invention relates to a DNA sequence of the 5' flanking region of the 5-HT1A receptor gene, from about -3438 to about -393 (SEQ ID NO:1), wherein said sequence contains a mutation that results in an inhibition of protein-DNA interactions. The novel DNA sequence can be used as a genetic marker in a diagnostic or prognostic test for mental illnesses that involve the

serotonin system. This invention further relates to proteins, which bind to this region and the use of said proteins to develop therapeutics to treat depression and related illnesses that involve the serotonin system. this invention also relates to a glucocorticoid-responsive element located from about -393 to the ATG initiation codon of the 5-HT1A receptor gene.--

Please replace the paragraph spanning page 14, line 18 through page 15, line 5, with the following paragraph:

--Blood samples from depressed patients were collected following extensive characterization of the patients for clinical drug trial. Documentation of the patients tested is included in Appendix 1. DNA samples from a random pool of normal individuals were also collected. The blood samples were either amplified directly or subjected to DNA extraction before amplification using optimal PCR conditions and primers. DNA extraction from whole blood samples was done using the Split Second DNA Preparation Kit (Boehringer Mannheim). When used directly, diluted blood samples were, prior to PCR amplification, subjected to three heat and cool cycles at 95°C and 55°C. PCR primers were designed to amplify a -718 bp fragment of the human 5-TH1A 5'-flanking region from -1593 to -876 bp of the initial ATG codon. The sense primer had the following sequence: 5'-GTGGCGAACATAAAACCTCA-3' (SEQ ID NO:3), and the antisense primer had the following sequence: 5'-TTCTTAAATCGTGTCAGCATC-3' (SEQ ID NO:4). PCR products were electrophoresed on a 1.0% agarose gel and DNA bands were purified, free of oligonucleotide primers, using the QIAEX II Gel Extraction Kit (Qiagen). Purified DNA was then heat-denatured at 95°C and snap-cooled in an ethanol/dry ice bath followed by a 30-min. annealing with PCR primers. Preparation was then sequenced using the Sanger dideoxy termination method (T7 sequencing kit, Pharmacia biotech).--

On page 19, please replace the paragraph spanning lines 3-22 with the following paragraph:

--The identification of a polymorphic change that correlates with major depression raises the important question of whether the -1017 bp region has functional activity. This region participates in the cell-specific basal repression of the 5-HT1A receptor gene based on its general location. Functional activity is demonstrated by the presence of a complex in nuclear protein extracts that

binds specifically to a 31-bp region flanking -1017 bp (Fig. 6). As detected by gel mobility shift assay, in the presence of nuclear extract from raphe RN46A cells several complexes were detected compared to without extract (lane 1). However, only the complex indicated was susceptible to competition with unlabeled specific 31-bp oligonucleotide, but not by an unrelated oligonucleotide, indicating a specific interaction. The other complexes may represent high capacity/low affinity interactions with the poly-A repeat segment of the 31-bp oligonucleotide. Thus, RN46A cells contain a specific nuclear complex that interacts with the -1017-bp region of the 5-HT1A receptor. Within the sequence flanking the C-G site (double-underlined) is a palindrome indicated in bold 5'-**AA<u>C</u>GAAGAC**NNNNNNN**GTCTTCTT**-3' (SEQ ID NO:2). The palindrome forms a structure that is recognized by DNA binding proteins. For example, steroid receptors recognize palindromic sequences as specific DNA binding sites (Evans, 1988). The C-G mutation may alter the stability of protein-DNA interactions at this site resulting in a change in 5-HT1A receptor expression or regulation.--

REMARKS

Enclosed are paper and computer readable form of the Sequence Listing. Applicants' agent hereby asserts that the content of the paper and computer readable copies of SEQ ID NO:1 through SEQ ID NO:7 submitted herewith are identical and include no new matter.

The specification has also been amended to insert the priority claim and to properly reference the sequences as they appear throughout the text. These amendments are made so that the application conforms to the requirements of 37 CFR 1.821-1.825 and add no new matter.

Respectfully submitted,

SHERIDAN ROSS P.C.

By: Angela Dallas

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Denver, CO 80202-5141
(303) 863-9700

Date: November 4, 2002

Marked Version Showing Amendments

In the Specification:

The following new subheading and paragraph have been added on page 1 following the title:

--CROSS-REFERENCE TO RELATED APPLICATIONS

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